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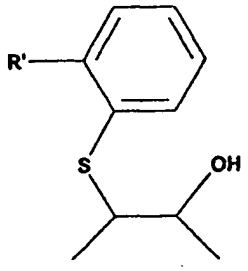
(54) Title: PHOTOCHEMICAL PROCESS FOR MAKING 1-DEOXY-2-KETO DERIVATIVES

(57) Abstract

A method for converting an epoxy or hydroxy moiety to a 1-deoxy-2-keto moiety is described which includes the steps of (a) providing a compound comprising an epoxy or hydroxy moiety having general structure (1a) or -CH(X)CH(OH)- (where X is a leaving group), (b) reacting the epoxy or hydroxy moiety with a thiophenol having attached thereon a radical generating substituent to produce a 1-phenylsulfide-2-hydroxy moiety having general structure (1b), and (c) irradiating the 1-phenylsulfide-2-hydroxy moiety with UV or near-UV radiation to convert the 1-phenylsulfide-2-hydroxy moiety to a 1-deoxy-2-keto moiety. The process is particularly useful for modifying the cyclic peptide ring systen of Echinocandin-type compounds containing a 1,2-diol moiety to produce new keto analogs.



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PHOTOCHEMICAL PROCESS FOR MAKING 1-DEOXY-2-KETO DERIVATIVES

TECHNICAL FIELD

The present invention relates to a photochemical process for the conversion of an epoxy or hydroxy moiety to a 1-deoxy-2-keto moiety. In particular, the invention relates to the conversion of the 1,2-diol moiety of an Echinocandin compound to the respective 1-deoxy-2-keto analog.

BACKGROUND ART

Macromolecules and in particular cyclic peptides such as those related to the antifungal agent Echinocandin B (ECB) can be very difficult to modify. Echinocandin B is a natural product with antifungal activity that has been modified in the past in a variety of ways. For example, simple derivatives have been made including dihydro-and tetrahydro-reduction products and modification of active groups pendant from the ring nucleus. The most common approach has been replacement of the N-acyl side chain. For example, U.S. Patent Nos. 4,293,489; 4,320,052; 5,166,135; and 5,541,160; and EP 359529; 448353; 447186; 462531; and 561,639 describe a variety of N-acyl derivatized echinocandin-type compounds that provide varying degrees of antifungal and antiprotozoal activities.

Other modifications have included acylation of the hydroxyl group of the pendant phenolic group. For example, GB 2,242,194; and EP 448343; 448354; 503960 and 525889 describe the introduction of acyl, phosphono and sulfo radicals having a charged group at neutral pH to impart water solubility.

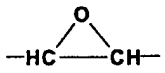
GB 2,241,956 and EP 448355 describe hydrogen-reduction products of cyclohexapeptide compounds.

Derivatization of cyclopeptide antifungal compounds has not only been limited by the number of active groups pendant from the cyclopeptide nucleus but also by the instability of the hemiaminal hydroxyl group of the ornithine peptide

unit. Therefore, there is a need to provide more stable intermediates so that a wider variety of derivatives can be prepared and tested for antifungal activity.

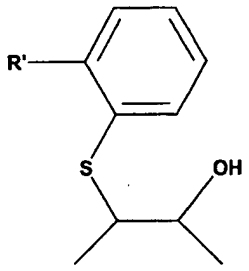
DISCLOSURE OF THE INVENTION

The present invention provides a method for converting an epoxy or hydroxy moiety to a 1-deoxy-2-keto moiety which includes the steps of (a) providing a compound comprising an epoxy or hydroxy moiety having the general structure 1a,



1a

or -CH(X)CH(OH)-where X is a leaving group, (b) reacting the epoxy or hydroxy moiety with a thiophenol having attached thereon a radical generating substituent (e.g., iodo, diazonium, bromo, etc.) to produce a 1-phenylsulfide-2-hydroxy moiety having the general structure 1b,



1b

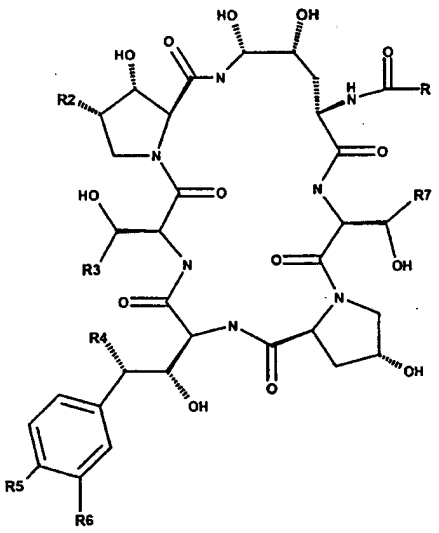
where R' is a radical generating substituent, and (c) irradiating the 1-phenylsulfide-2-hydroxy moiety with Ultraviolet (UV) or near-UV radiation (in the presence of *bis*-tributylin when R' is iodo or bromo) to convert the 1-phenylsulfide-2-hydroxy moiety to a 1-deoxy-2-keto moiety. The inventive process is particularly useful for modifying the cyclic peptide ring system of echinocandin-type compounds containing a 1,2-diol moiety to produce new keto analogs.

As used herein, the term "leaving group" refers to a substituent having sufficient lability such that it can be substituted by a nucleophile (i.e., a thiophenol). The lability of a particular substituent will vary depending upon

substituents on the same and/or adjacent carbon atoms and the nature of the leaving group. Those skilled in the art will appreciate the types of leaving groups capable of substitution by a thiophenol.

The term "radical generating substituent" refers to a substituent that, upon irradiation to UV or near-UV radiation, cleaves from the phenyl ring to which it is attached and generates an aryl radical. Depending upon the particular substituent, a sensitizing agent and/or photoinitiator can be used to initiate the radical cleavage.

The term "echinocandin-type compounds" refers to compounds having the following general structure including any simple derivatives thereof:



wherein R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group; R2 is -H or $-CH_3$; R3 is -H, $-CH_3$, $-CH_2CONH_2$ or $-CH_2CH_2NH_2$; R4 is -H or -OH; R5 is -OH, $-OPO_3H_2$, $-OPO_3HCH_3$, $-OPO_2HCH_3$, or $-OSO_3H$; R6 is -H, -OH, or $-OSO_3H$; R7 is -H or $-CH_3$; and pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

The term "alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1} containing from 1 to 30 carbon atoms unless otherwise indicated. The alkane radical can be straight, branched, cyclic, or multi-cyclic. The alkane

radical can be substituted or unsubstituted. Similarly, the alkyl portion of an alkoxy group or alkanoate has the same definition as above.

The term "alkenyl" refers to an acyclic hydrocarbon containing at least one carbon-carbon double bond. The alkene radical can be straight, branched, cyclic, or multi-cyclic. The alkene radical can be substituted or unsubstituted.

The term "alkynyl" refers to an acyclic hydrocarbon containing at least one carbon-carbon triple bond. The alkyne radical can be straight, or branched. The alkyne radical can be substituted or unsubstituted.

The term "aryl" refers to aromatic moieties having single (e.g., phenyl) or fused ring systems (e.g., naphthalene, anthracene, phenanthrene, etc.). The aryl groups can be substituted or unsubstituted. Substituted aryl groups include a chain of aromatic moieties (e.g., biphenyl, terphenyl, phenylnaphthalyl, etc.)

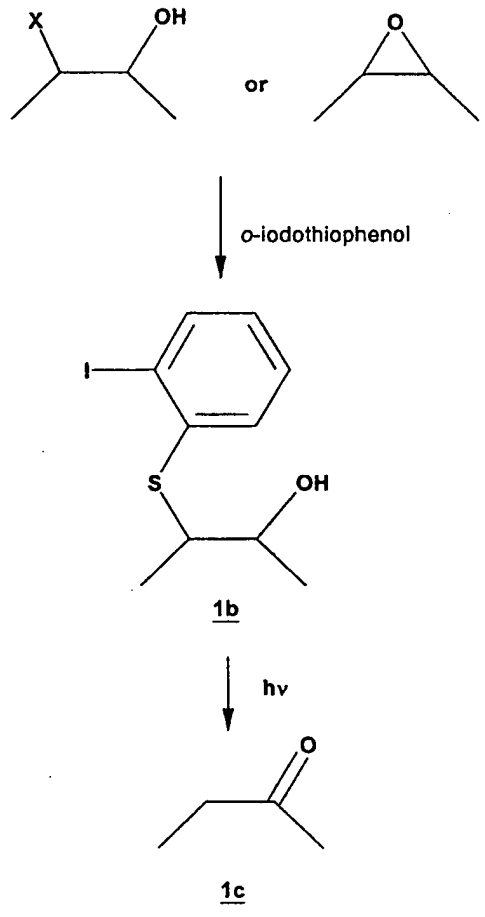
The term "heteroaryl" refers to aromatic moieties containing at least one heteratom within the aromatic ring system (e.g., pyrrole, pyridine, indole, thiophene, furan, benzofuran, imidazole, pyrimidine, purine, benzimidazole, quinoline, etc.). The aromatic moiety can consist of a single or fused ring system. The heteroaryl groups can be substituted or unsubstituted.

Within the field of organic chemistry and particularly within the field of organic biochemistry, it is widely understood that significant substitution of compounds is tolerated or even useful. In the present invention, for example, the term alkyl group allows for substituents which are classic alkyls, such as methyl, ethyl, propyl, *n*-butyl, *i*-butyl, *t*-butyl, hexyl, isooctyl, dodecyl, stearyl, etc. The term group specifically envisions and allows for substitutions on alkyls which are common in the art, such as hydroxy, halogen, alkoxy, carbonyl, keto, ester, carbamato, etc., as well as including the unsubstituted alkyl moiety. However, it is generally understood by those skilled in the art that the substituents should be selected so as to not adversely affect the pharmacological characteristics of the compound or adversely interfere with the use of the medicament. The same is true for each of the other groups (i.e., aryl, alkynyl, alkenyl, heteroaryl). Suitable substituents for any of the groups defined above include alkyl, alkenyl, alkynyl, aryl, halo, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, mono- and di-

alkyl amino, quaternary ammonium salts, aminoalkoxy, hydroxyalkylamino, aminoalkylthio, carbamyl, carbonyl, carboxy, glycolyl, glycyl, hydrazino, guanyl, and combinations thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

The following general synthetic scheme illustrates the conversion of a hydroxy moiety having the general structure (1a) to produce a o-iodophenylsulfide derivative (1b) which is then converted to the corresponding 1-deoxy-2-keto moiety (1c). The iodo substituent serves as a radical source; therefore, other radical generating substituents, such as bromides and diazonium ions, can be used as well.

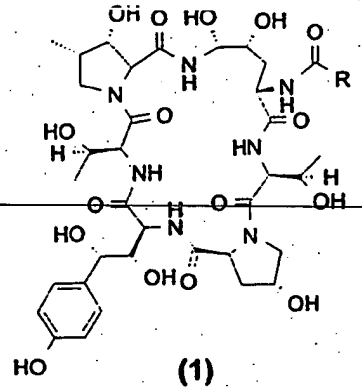


1b

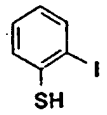
1c

The inventive method is particularly useful for modifying a 1,2-diol moiety of an ornithine unit in a cyclic peptide to produce the corresponding 1-deoxy-2-keto analog as outlined in the following synthetic scheme. The leaving group (X) in this particular practice of the invention is a hydroxy group. The hydroxy group of the ornithine group is labile (i.e., capable of acting as a leaving group and being substituted by the thiophenol) since it is part of a hemiaminal functionality.

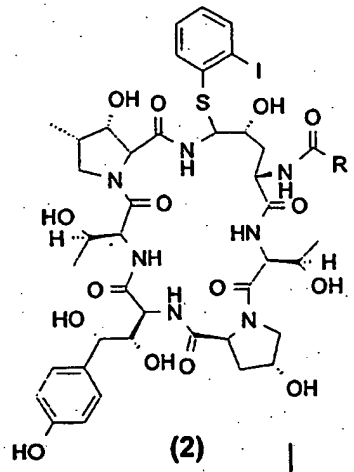
For illustrative purposes, the following synthetic scheme starts with a specific echinocandin derivative. However, it is to be understood that one could begin with any natural product, semi-synthetic or synthetic cyclopeptide compound in which a thiophenol derivative can be selectively introduced next to a hydroxyl group. The term "natural product" refers to those secondary metabolites, usually of relatively complex structure, which are of more restricted distribution and more characteristic of a specific source in nature. Suitable natural product starting materials belonging to the Echinocandin cyclopeptide family include Echinocandin B, Echinocandin C, Echinocandin D, Aculeacin Aγ, Mulundocandin, Sporiofungin A, Pneumocandin A_0, WF11899A, and Pneumocandin B_0.



(1)

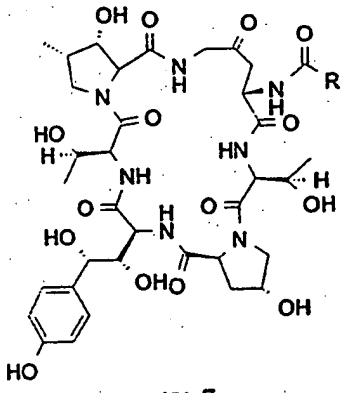


TFA, MeCN



(2)

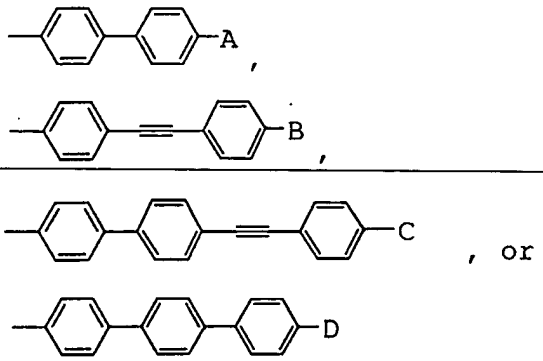
$(Bu_3Sn)_2$ hυ (300nm)
t-BuOH, acetone



(3)

The cyclic peptides used in the present invention can be produced by culturing various microorganisms. Suitable natural product starting materials belonging to the echinocandin cyclic peptide family include Echinocandin B, Echinocandin C, Echinocandin D, Aculeacin Aγ, Mulundocandin, Sporiofungin A, Pneumocandin A_0, WF11899A, and Pneumocandin B_0. In general, the cyclic peptides can be characterized as a cyclic hexapeptide nucleus with an acylated amino group on one of the amino acids. The amino group on the naturally-occurring cyclic peptide is typically acylated with a fatty acid group forming a side chain off the nucleus. Examples of naturally-occurring acyl groups include linoleoyl (Echinocandin B, C and D), palmitoyl (Aculeacin Aγ and WF11899A), stearoyl, 12-methylmyristoyl (Mulundocandin), 10,12-dimethylmyristoyl (Sporiofungin A and Pneumocandin A_0) and the like.

Semi-synthetic derivatives can be prepared by removing the fatty acid side chain from the cyclic peptide nucleus to produce a free amino group (i.e., no pendant acyl group -C(O)R). The free amine is then reacylated with a suitable acyl group. For example, the echinocandin B nucleus has been re-acylated with certain nonnaturally occurring side chain moieties to provide a number of antifungal agents. See, i.e., U.S. Patent No. 4,293,489. Those skilled in the art will appreciate that the N-acyl side chain encompasses a variety of side chain moieties known in the art. Suitable side chain moieties include substituted and unsubstituted alkyl groups, alkenyl groups, alkynyl groups, aryl groups, heteroaryl groups and combinations thereof. Preferably, the side chain contains both a linearly rigid section and a flexible alkyl section to maximize antifungal potency. Representative examples of preferred acyl side chains include R groups having the following structures:



, or

where A, B, C and D are independently hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkylthio, halo, or

-O-$(CH_2)_m$-[O-$(CH_2)_n$]$_p$-O-(C_1-C_{12} alkyl) or -O-$(CH_2)_q$-X-E;

m is 2, 3 or 4; n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4;

X is pyrrolidino, piperidino or piperazino; and E is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl.

The iodophenylsulfide derivative (2) is synthesized from the cyclopeptide (1) using the general procedures described in WO 96/24613. Compound (1) is reacted with *o*-iodothiophenol in acetonitrile and trifluoroacetic acid (TFA). According to WO 96/24613, the best yield is achieved when 5-25% TFA in acetonitrile is used and 3 to 5 equivalents of the thiophenol. The preferred conditions for the sulfide formation were determined to be 5 equivalents thiophenol in 10% TFA/acetonitrile at 0°C. The thiol can be made from the disulphide as described in *Synth. Comm.*, 16(7), 819-825 (1986).

The sulfide is then irradiated in a Rayonet mini reactor, 8 bulb, Model RMR-600 at 300 nm in the presence of bis-tributyltin in t-butyl alcohol/acetone to produce Compound (3). Other UV irradiation sources can be used for the photolysis reaction. The reaction time can vary depending upon the output of the particular radiation source used. The reaction can be run under normal atmospheric conditions. An inert atmosphere is not necessary, but could be used if desired. The reaction is generally run at room temperature; however, during the reaction it is not uncommon for the mixture to increase in temperature due to heat output from the irradiation unit. The reaction time appears to be related to the

concentration of the bis-tributyltin. Higher concentrations (74 equivalents) gave rise to fast reaction times (i.e., about 30 minutes) while lower concentrations (0.5 equivalents) required longer reaction times (in excess of 5 hours).

The photolysis can be run in a variety of solvents. Generally, the solubility of the compound being irradiated and the absence of an abstractable hydrogen are the key factors used to determine the optimum solvent(s). Suitable solvents include t-butyl alcohol, acetone, acetonitrile, benzene, hydrocarbons, etc. Less preferred solvents include THF, ethyl acetate, dioxane, methanol, ethanol, methylene chloride and chloroform. A preferred solvent is 1:3.5 *t*-butyl alcohol:acetone mixture.

The reaction mixture is typically contained in a UV or semi-UV transparent vessel. The vessel is chosen such that sufficient radiation is allowed to penetrate the vessel wall so that it can be absorbed by the suspended or dissolved compound. Suitable vessels include borosilicate and quartz enclosures. Vessels having large surface areas are preferred.

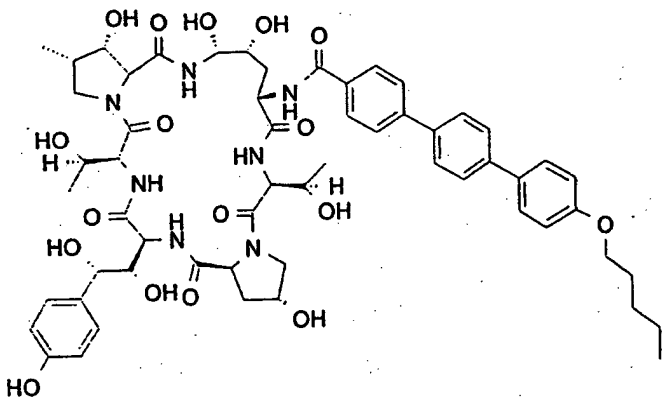
The compounds of the present invention can be isolated and used per se or in the form of their pharmaceutically acceptable salt or hydrate. The term "pharmaceutically acceptable salt" refers to non-toxic acid addition salts derived from inorganic and organic acids. Suitable salt derivatives include halides, thiocyanates, sulfates, bisulfates, sulfites, bisulfites, arylsulfonates, alkylsulfates, phosphonates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphonates, alkanoates, cycloalkylalkanoates, arylalkonates, adipates, alginates, aspartate, benzoates, fumarates, glucoheptanoates, glycerophosphates, lactates, maleates, nicotinates, oxalates, palmitates, pectinates, picrates, pivalates, succinates, tartarates, citrates, camphorates, camphorsulfonates, digluconates, and the like.

The 1-deoxy-2-keto compound can be further modified by reaction with common reagents known to those skilled in the art to produce various derivatives. For example, the keto group can be converted to an alkenyl group (i.e., via a Wittig reaction) or a diazo group (i.e., reaction with a hydrazine), etc.

The following examples are ment to illustrate but not to limit the invention. All illustarte but not limit the invention. All references cited herein, both supra and infra, are hereby incorporated by reference herein.

EXAMPLES

Unless indicated otherwise, all chemicals can be acquired from Aldrich Chemical (Milwaukee, WI).

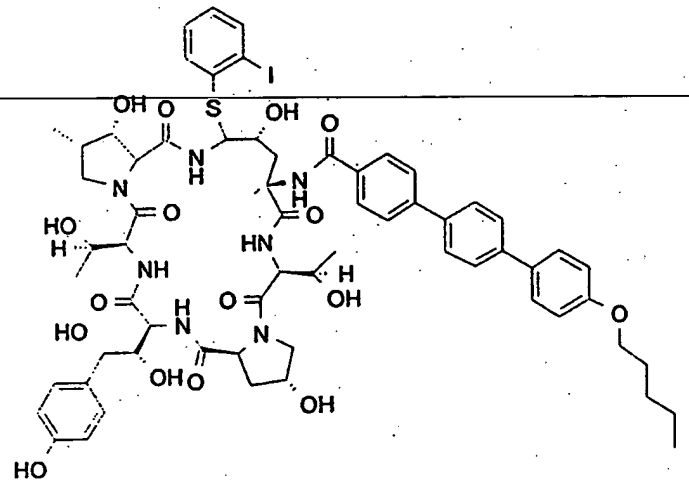


1a

Compound 1a can be prepared as described in EP 561639. Echinocandin B (also known as A-30912A) is deacylated to provide the echinocandin B nucleus with the deacylase produced by the organism *Actinoplanes utahensis* as described in U.S. Patent Nos. 4,293,482 and 4,303,716, incorporated herein by reference. The amino nuclei obtained by the N-deacylation is then acylated with the 2,4,5-trichlorophenol ester of p-(p-n-pentoxybiphenyl)benzoic acid by employing known amino acylation procedures to provide the N-acylated product.

The following set of examples illustrate the general reaction conditions for converting the dihydroxy moiety of an ornithine peptide unit of a cyclohexapeptide nucleus to a 1-deoxy-2-keto moiety.

Preparation of Key Intermediates

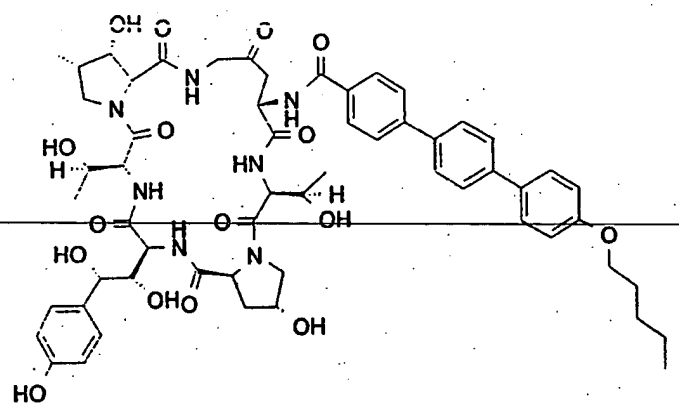


I-2

Preparation of thioether intermediate I-2

A 50 ml round bottom flask was charged with 462 mg Compound 1a (0.406 mmol) in 17.5 ml acetonitrile under a dry nitrogen atmosphere. The mixture was cooled to -5°C with a NaCl ice bath followed by the addition of a solution of 2-iodothiophenol (502 mg, 2.13 mmol) in 5 ml methanol. Trifluoroacetic acid (2.761 g, 24.22 mmol) was added dropwise via a syringe over 20 minutes. After the addition, HPLC indicated that little Compound 1a remained. The reaction was quenched by adding 42 ml of cold water to the cold reaction mixture over an hour. The insoluble solid was transferred using dioxane and the solution was lyophilized down to yield 666 mg of a solid. The solid was taken up in approximately 6 ml of dioxane and 2 ml of water and purified by reverse phase prep HPLC. Lyophilization of the fractions gave 246 mg of product having a FAB MS M+ at 1358.7.

Example 1 illustrates the general reaction conditions for converting the thioether intermediate I-2 to its corresponding ketone derivative 1-3.



1-3

Example 1

Intermediate I-2 was dissolved in 16 ml t-butylalcohol and 56 ml acetone by sonication at 40°C for 30 minutes. Hexabutylditin (40 mg, 0.029 mmol) was added to the solution and then transferred into an 80 ml quartz irradiation tube. The mixture was irradiated for one hour and 45 minutes at 300 nm in a Rayonet Model RMR-600 irradiation unit. The reaction mixtures from six individual runs as described above were combined and the solvent removed via a rotary evaporator. The resultant oil was dissolved in methanol and extracted three times with hexanes. The methanol was reconcentrated, the oil dissolved in a small amount of methanol and stirred rapidly as diethyl ether was slowly added upon which a precipitate formed. The solid was dissolved in a small amount of 6:1 methanol/dioxane and purified by reverse phase HPLC. The fractions were lyophilized to give 69 mg of a white powder (35% yield) having a FAB MS M+ peak at 1122.7. The 500 MHz ^{1}H and ^{13}C NMR were consistent with the structure 1-3.

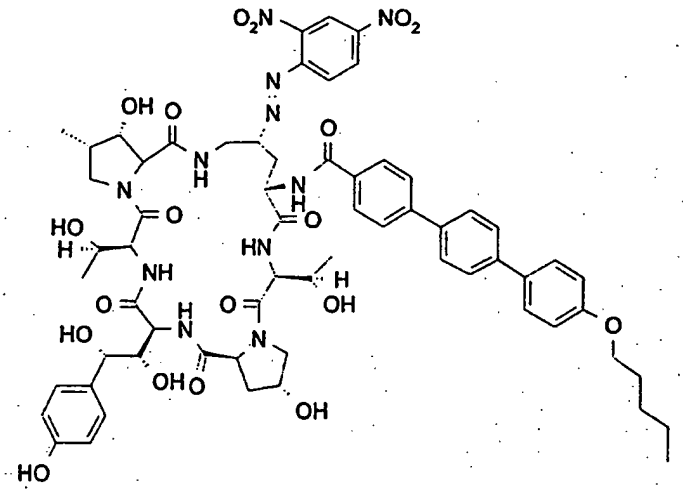
Examples 2 and 3 illustrate modifications of keto compound 1-3 to provide additional derivatives of echinocandin-type compounds.

Example 2

A stock solution of 2,4-dinitrophenyl hydrazine was prepared according to Behforouz, M., et al., "2,4-Dinitrophenylhydrazones: A Modified Method for the Preparation of these Derivatives and an Explanation of Previous Conflicting Results," *J. Org. Chem.*, 50, 1186-1189 (1985). 2,4-dinitrophenyl hydrazine (271

mg) was dissolved in 1.30 ml concentrated sulfuric acid. With stirring, 1.9 ml water and 6.75 ml 95% ethanol was added to the solution.

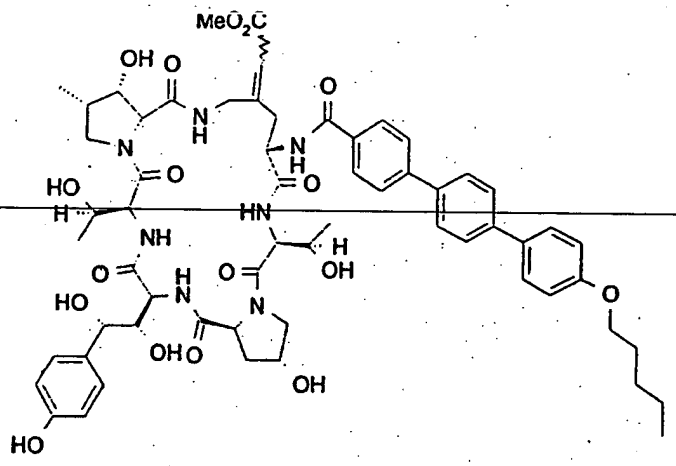
Compound 1-3 (1.0 mg, 0.00134 mmol) was dissolved in approximately 200 µL 95% ethanol. This solution was then added to 20 µL of the 2,4-dinitrophenyl hydrazine stock solution. The mixture was allowed to stir for about 3 minutes. HPLC indicated a new product had formed having a MS M+ that is consistent with the following structure 2-1.



2-1

Example 3

Compound 1-3 (1 mg, 0.0009 mmol) and ethylacetate triphenylphosphine ylid (0.37 mg, 0.0011 mmol) in 1 ml of THF were mixed in a 1 dram vial. The mixture was stirred at 45°C overnight. HPLC indicated two products were forming. The heat was increased to 70°-75°C. Little or no change was noted after 2-3 hours so the mixture was allowed to stir at that temperature overnight. HPLC indicated two products and 90% consumption of the Compound 1-3. Both products had the same MS M^+ which was consistent with the following structure 3-1 (cis/trans isomers).

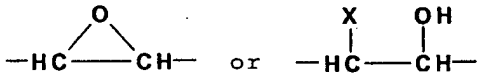


3-1

CLAIMS

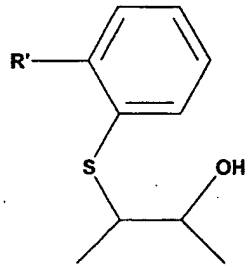
1. A method for converting an epoxy or hydroxy moiety to a 1-deoxy-2-keto moiety comprising the steps of:

(a) providing a compound comprising an epoxy or hydroxy moiety having the general structure



where X is a leaving group;

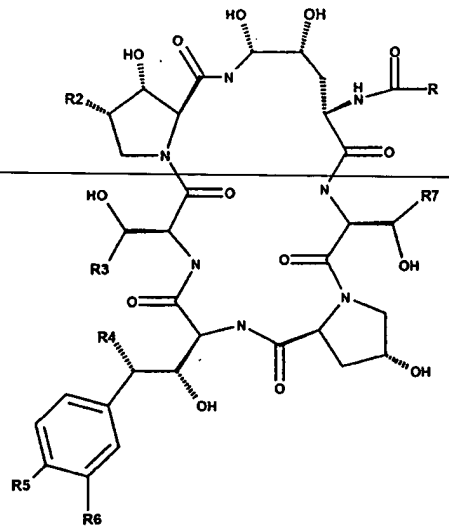
(b) reacting said epoxy or hydroxy moiety with a thiophenol having attached thereon a radical generating substituent to produce a 1-phenylsulfide-2-hydroxy moiety having the following general structure 1b; and



1b

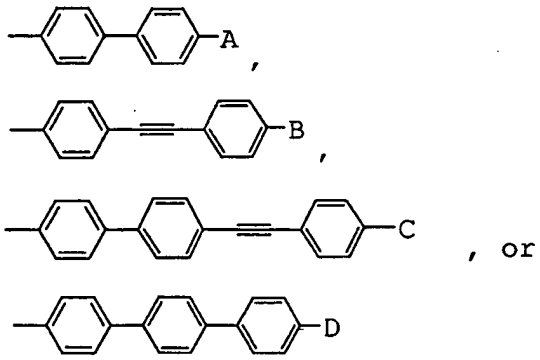
(c) irradiating said 1-phenylsulfide-2-hydroxy moiety with UV or near-UV radiation to convert said 1-phenylsulfide-2-hydroxy moiety to a 1-deoxy-2-keto moiety.

2. The process of Claim 1 wherein said compound of step (a) is represented by the following structure:



wherein R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group; R2 is -H or $-CH_3$; R3 is -H, $-CH_3$, $-CH_2CONH_2$ or $-CH_2CH_2NH_2$; R4 is -H or -OH; R5 is -OH, $-OPO_3H_2$, $-OPO_3HCH_3$, $-OPO_2HCH_3$, or $-OSO_3H$; R6 is -H, -OH, or $-OSO_3H$; and R7 is -H or $-CH_3$; and pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

3. The process of Claim 2 wherein R is



where A, B, C and D are independently hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkylthio, halo, or

$-O-(CH_2)_m-[O-(CH_2)_n]_p-O-(C_1-C_{12}$ alkyl) or $-O-(CH_2)_q-X-E$; m is 2, 3 or 4; n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4; X is pyrrolidino, piperidino or piperazino; and E is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl.

4. The process of Claim 2 wherein R is selected from the group consisting of linolenyl, palmityl, stearyl, 12-methylmyristyl, and 10,12-dimethylmyristyl.

5. The process of Claim 2 wherein said thiophenol is *o*-iodothiophenol.

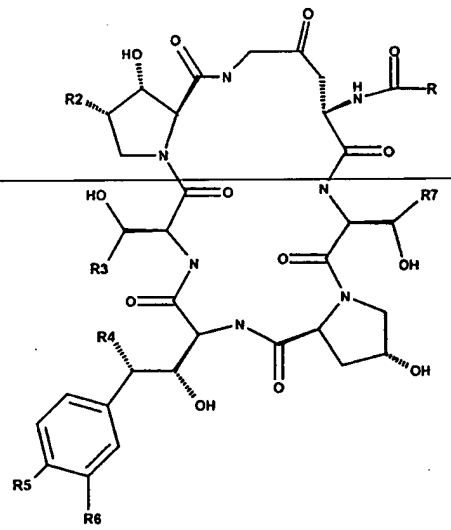
6. The process of Claim 5 wherein said reacting step (b) is run in the presence of 5-25% trifluoroacetic acid in acetonitrile and 3 to 5 equivalents of said *o*-iodothiophenol.

7. The process of Claim 5 wherein said reacting step (b) is run in the presence of 10% trifluoroacetic acid in acetonitrile at 0°C and 5 equivalents of said *o*-iodothiophenol.

8. The process of Claim 5 wherein said irradiating step (c) is run in the presence of *bis*-tributyltin.

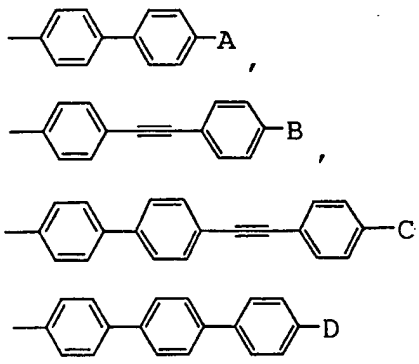
9. The process of Claim 5 wherein said irradiating step (c) is run in a 1:3.5 *t*-butyl alcohol:acetone solvent mixture.

10. A compound represented by the following general structure:



wherein R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group; R2 is -H or $-CH_3$; R3 is -H, $-CH_3$, $-CH_2CONH_2$ or $-CH_2CH_2NH_2$; R4 is -H or -OH; R5 is -OH, $-OPO_3H_2$, $-OPO_3HCH_3$, $-OPO_2HCH_3$, or $-OSO_3H$; R6 is -H, -OH, or $-OSO_3H$; and R7 is -H or $-CH_3$; and pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

11. The compound of Claim 10 wherein R is



, or

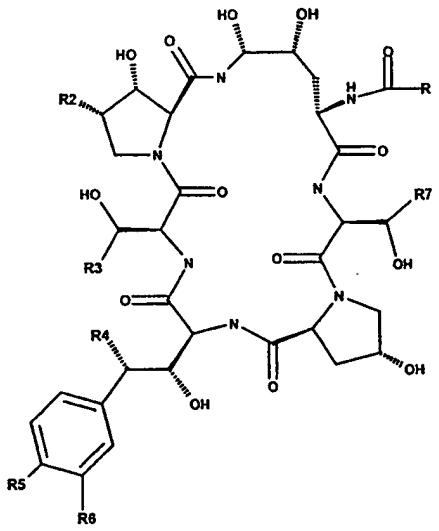
where A, B, C and D are independently hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkylthio, halo, or -O-

$(CH_2)_m$-[O-$(CH_2)_n$]$_p$-O-(C_1-C_{12} alkyl) or -O-$(CH_2)_q$-X-E; m is 2, 3 or 4; n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4; X is pyrrolidino, piperidino or piperazino; and E is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl.

12. The compound of Claim 10 wherein R is selected from the group consisting of linolenyl, palmityl, stearyl, 12-methylmyristyl, and 10,12-dimethylmyristyl.

13. A 1-deoxy-2-keto compound prepared by a process comprising the steps of:

(a) providing a 1,2-diol compound represented by the structure

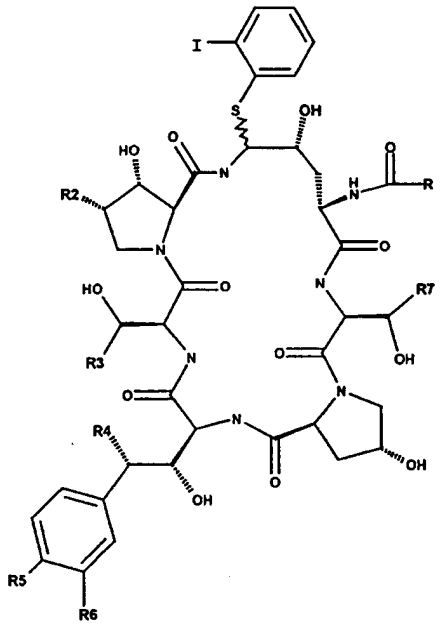


wherein R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group; R2 is -H or -CH_3; R3 is -H, -CH_3, -CH_2CONH_2 or -$CH_2CH_2NH_2$; R4 is -H or -OH; R5 is -OH, -OPO_3H_2,

$-OPO_3HCH_3$, $-OPO_2HCH_3$, or $-OSO_3H$; R6 is -H,

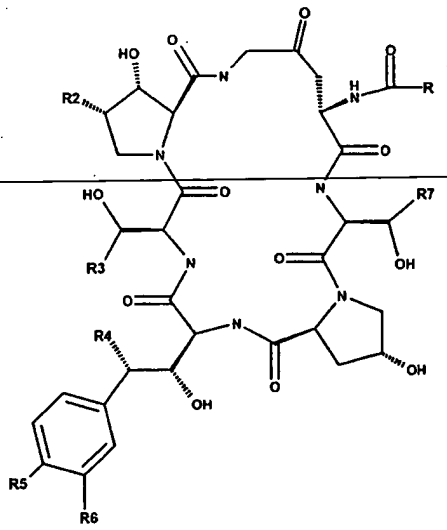
-OH, or $-OSO_3H$; and R7 is -H or $-CH_3$;

(b) reacting said 1,2-diol compound with *o*-iodo-thiophenol to produce a sulfide derivative having the general structure



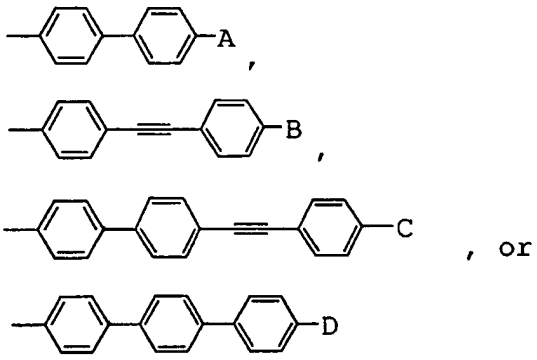
wherein R, R2, R3, R4, R5, R6 and R7 have the same meaning as in step a); and

(c) irradiating said sulfide derivative with UV radiation to convert said sulfide derivative to said 1-deoxy-2-keto compound having the general structure



wherein R, R2, R3, R4, R5, R6 and R7 have the same meaning as above and pharmaceutically acceptable salts, esters, hydrates or solvates thereof.

14. The 1-deoxy-2-keto compound of Claim 13 wherein R is



where A, B, C and D are independently hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkylthio, halo, or -O-$(CH_2)_m$-$[O$-$(CH_2)_n]_p$-O-(C_1-C_{12} alkyl) or -O-$(CH_2)_q$-X-E; m is 2, 3 or 4; n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4; X is pyrrolidino,

piperidino or piperazino; and E is hydrogen, C_1-C_{12} alkyl, C_3-C_{12} cycloalkyl, benzyl or C_3-C_{12} cycloalkylmethyl.

15. The 1-deoxy-2-keto compound of Claim 13 wherein R is selected from the group consisting of linolenyl, palmityl, stearyl, 12-methylmyristyl, and 10,12-dimethylmyristyl.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 99/25301

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07B41/06 C07K7/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07B C07K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	O. PIVA: "Direct conversion of bromohydrins to ketones" TETRAHEDRON LETTERS, vol. 33, no. 18, 28 April 1992 (1992-04-28), pages 2459-2460, XP000272398 OXFORD GB the whole document	1
A	WO 96 24613 A (MERCK) 15 August 1996 (1996-08-15) cited in the application claims	1,10,13
A	EP 0 448 353 A (MERCK) 25 September 1991 (1991-09-25) cited in the application claims; examples	10,13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
29 February 2000	08/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wright, M

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INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/US 99/25301

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 29716 A (HOECHST MARION ROUSSEL) 17 June 1999 (1999-06-17) page 8, line 23 to page 10, line 38; page 12, lines 23-36; page 19, lines 22-33; page 21, lines 9-22	10-15

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/US 99/25301

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